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EXAMINER	
KOLKER, DANIEL E	

ART UNIT	PAPER NUMBER
1649	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/587,535	CARROLL ET AL.	
	Examiner	Art Unit	
	Daniel Kolker	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/22/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1 – 16 are pending and under examination in the instant office action.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 8 – 13 and 15 – 16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for decreasing pain which accompanies cardiovascular conditions, does not reasonably provide enablement for treatment of the cardiovascular conditions themselves. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

There are many factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue. These factors include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (FED. Cir. 1988).

In the instant case, the nature of the invention is complex. Claims 8 – 12 are drawn to treatment of cardiovascular diseases; claims 13 and 15 – 16 encompass treating any and all diseases, independent of their etiology. Cardiovascular diseases are caused by a multitude of different factors, including genetics, diet, and exercise, among others. The instant claims require administration of botulinum toxin for treating cardiovascular diseases. Botulinum toxin prevents release of acetylcholine from neurons (specification, p. 2, paragraphs [10] – [11]). The art recognizes that cardiovascular diseases have many different treatments, but preventing release of acetylcholine is not among them. For example, Ellozy (2003. Mount Sinai Journal of Medicine 70:417-419) teaches that peripheral vascular disease, recited in claim 9, is effectively treated by stents which secrete sirolimus. Lafont (2003. Heart 89:1262-1267) teaches that

coronary artery disease is characterized by plaques within arteries, and remains difficult to treat, as those treatments which might loosen the plaque could easily result in thrombosis, which can be deadly. Knight (2003. Heart 89:1273-1278) teaches that coronary artery disease, recited in claim 9, can be treated with antiplatelet drugs such as aspirin ADP receptor antagonists, or glycoprotein IIb/IIa inhibitors.

The disclosure states that the various cardiovascular conditions can be treated by administration of botulinum toxin (paragraph [58] and following text) but provides no working examples of such. The examples in the specification fail to show treatment of these diseases by administration of the toxin. The examples disclose successful relief from pain, but do not show treatment of the disease states themselves. There is no indication that botulinum toxin decreases the size of coronary artery plaques or improves peripheral vascular disease. The art indicates that treatments other than blockade of acetylcholine release are important therapies for these cardiovascular diseases, and does not recognize the role of actylcholine release in treatment of the full scope of cardiovascular conditions. The skilled artisan would have to resort to a large degree of experimentation in order to determine which cardiovascular conditions are amenable to treatment by botulinum toxin, and then determine how to treat those diseases. Given that the specification shows no actual treatment of cardiovascular disease beyond relief from pain associated with those diseases, and the art does not support a mechanistic link between actylcholine and cardiovascular disease, as well as the fact that the specification offers no guidance as to how to achieve the stated result of treating cardiovascular conditions, the large degree of experimentation required by the skilled artisan would clearly be undue.

Additionally, the specification fails to provide adequate enablement for treatment of any and all diseases, as encompassed by independent claim 13. While the prior art recognized that certain diseases falling within the scope of dependent claim 14 are amenable to treatment with botulinum toxin (see for example Donovan U.S. Patent Application Publication 2001/0023243, who teaches administration of the toxin for treatment of pancreatitis) the specification fails to provide adequate guidance or working examples for treatment of all diseases. Note claim 13 is not limited to any particular disease. The broadest reasonable interpretation of the claim includes treatment of HIV, influenza, malaria, and cancer by administering the toxin to the celiac plexus. As none of these conditions are caused or characterized by abnormal acetylcholine release, it is not reasonable that botulinum toxin would be efficacious in their treatment. Given that there are no working examples of treating HIV, malaria, influenza, or cancer in the

specification, and that there is no guidance as to how to treat these diseases with botulinum toxin, and the skilled artisan would recognize that they would be highly unlikely to treat these diseases, the large amount of experimentation required to determine the effective doses of the toxin for such treatment would be undue.

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 14 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 14 recites the limitation "said condition" in line 1. There is insufficient antecedent basis for this limitation in the claim. Amendment to "said disease" is recommended, as "disease" not "condition" is recited in claim 13.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 13 – 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Donovan (U.S. Patent Application Publication 2001/0023243, published 21 September 2001).

Donovan teaches administration of botulinum toxin to the celiac plexus (see p. 9 paragraph [0090]). The reference teaches that botulinum type A is to be used (see paragraph [0095]; see also paragraph [0062] which teaches that "the neurotoxin" referred to in the publication is most preferably botulinum toxin type A). Donovan clearly teaches administration to human patients (see paragraph [0080]). Thus the reference teaches every element of claim 13. Claim 14 is rejected as Donovan teaches that the method is to be used for treating pancreatitis (paragraph [0090]). Claim 15 is rejected as Donovan specifically teaches type A is to be used. Claim 16 is rejected as Donovan teaches many doses within the range are suitable for administration to humans (see paragraphs [0035] – [0048], paragraph [0080]).

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1 – 3 and 5 – 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kim (2002. Autonomic Neuroscience 102:8-12; cited on IDS filed 22 February 2007).

Kim teaches sympathetically mediated chronic pain is mediated by the sympathetic ganglion (see p. 8 first paragraph). The reference teaches administration of botulinum toxin type A, recited in claims 1 and 2. The reference teaches that the dose used was 2 - 10 units per kilogram of body weight, administered to rabbits which is within the range recited in claim 3, given that rabbits weigh less than 30 kg. The reference teaches administration to the superior cervical ganglion as recited in claim 5 - 6. However Kim does not teach administration to humans, as recited in claim 1.

It would have been obvious to one of ordinary skill in the art to modify the method of Kim et al. to treat humans in pain, with a reasonable expectation of success. The motivation to do so would be to effectively treat pain in humans. It is reasonable to expect success as the rabbits used by Kim are a model of human physiology, the reference by Kim teaches the appropriate dose, and Kim suggests that the side effects are minimal and that the toxin should be used for treatment of sympathetic pain. Additionally, Kim contemplates modifications of the method for clinical use, which implies treatment of humans, and specifically notes that the exact dose may have to be varied (see Kim, p. 11, last two paragraphs)

6. Claims 1 – 3 and 5 – 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kim (2002) as applied to claims 1 – 3 and 5 – 6 above, and further in view of Erickson (1993. Radiology 188:707-709).

The reasons why claims 1 – 3 and 5 – 6 are obvious over Kim are set forth above. However, Kim does not teach administering a local anesthetic as a sympathetic block and identifying chronic pain as being mediated by the sympathetic nervous system as recited in claim 7.

Erickson teaches methods of administering local anesthetic, including lidocaine, bupivarcaine, and buprenophrine as sympathetic blocks. The specific drugs are listed in the abstract, and the first paragraph of the Materials and Methods section teaches that the stellate ganglion, which is a sympathetic ganglion, was the target. Erickson teaches the method is successful in human patients, as recited in claim 1, and leads to pain relief, including complete pain relief which is more than 50% of the perceived pain as recited in claim 7 (see results section). Erickson teaches that the duration of relief is generally short, between one hour and three weeks. However Erickson does not teach administration of botulinum toxin as recited in claim 1.

It would have been obvious to one of ordinary skill in the art to include the step of administering a short-acting local anesthetic as a sympathetic block, as taught by Erickson, when performing the methods of claims 1 – 3, as suggested by Kim, thereby arriving at the invention of claim 7. The motivation to do so would be to ensure that the pain experienced by the patient is in fact mediated by the sympathetic ganglia. Performing this step would be advantageous, as it would ensure that those patients whose pain is not mediated by sympathetic ganglia will not be exposed to the toxin. Thus by performing the step taught by Erickson and recited in claim 7, the artisan would ensure identification of the patients most amenable to treatment.

7. Claims 1 – 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kim (2002) as applied to claims 1 – 3 and 5 – 6 above, and further in view of Brushey (U.S. Patent Application Publication 2001/0056275, published 27 December 2001).

The reasons why claims 1 – 3 and 5 – 6 are obvious over Kim are set forth above. However, Kim does not teach administration to the splanchnic nerve when pain is in the lower

extremities, as recited in claim 4.

Brushey teaches that when sympathetic pain is present in the lower extremities, the splanchnic nerve should be blocked (see paragraphs 0004 - 0005). However Brushey does not teach administration of botulinum toxin as recited in claim 1.

It would have been obvious to one of ordinary skill in the art to modify the method of Kim et al. such that when the pain is present in the lower extremities, the toxin would be given to block the splanchnic nerve. The motivation to do so would be to effectively block pain, as Brushey teaches this is the nerve to be blocked when pain is present in the lower extremity.

8. Claims 1 – 3, 5 – 6, and 8 – 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Henard (1982. Arch Mal Coeur 75(11):1317-1320, cited on IDS filed 22 February 2007) in view of Kim (2002).

Henrard teaches treatment of coronary vasospasm which is on point to claims 8 – 9. Henrard teaches that the spasms can be treated by homolateral thoracic sympathectomy, i.e. surgical removal of a sympathetic ganglion (see abstract translation on p. 1320). However Henrard does not teach administration of boutlinum toxin.

The reasons why claims 1 – 3 and 5 – 6 are obvious over Kim are set forth above. Kim teaches pain relief by administering botulinum toxin to a sympathetic ganglion, which is on point to claims 8 and 10, and teaches type A of the toxin as recited in claim 11 and doses as recited in claim 12. However, Kim does not teach administering botulinum toxin to patients with cardiovascular conditions as recited in claim 8, or the specific diseases recited in claim 9.

It would have been obvious to one of ordinary skill in the art to modify the method of Henrard by administering botulinum toxin to the sympathetic ganglion instead of removing the sympathetic ganglion, thereby arriving at the invention of claims 8 – 12. Henrard teaches that inactivating the ganglion by removal is sufficient for treatment of spasm, and using botulinum toxin for inactivation, as taught by Kim, would be advantageous as it would be less invasive.

Conclusion

9. No claim is allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel Kolker whose telephone number is (571) 272-3181. The examiner can normally be reached on Mon - Fri 8:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Patent Examiner

Daniel E. Kolker, Ph.D.
October 10, 2007